ARC-HPV Report Summary

Periodic Reporting for period 1 - ARC-HPV (Automated Raman spectral Cytology for detection of human papillomavirus (HPV) infection and cervical pre-cancer)

Reporting period: 2016-01-18 to 2018-01-17

Summary of the context and overall objectives of the project

Cervical cancer is the 4th most common cause of cancer death in women worldwide and the 7th most common cause of cancer death in females in Europe. Human papillomavirus (HPV) infection is very common in sexually active men and women. More than 100 different strains of HPVs have been identified and 14 of them (i.e., HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered as high risk. Most HPV infections (~90%) will self-resolve in two years but high risk HPV infection can cause chronic and persistent cellular changes. Persistent high-risk HPV infection can lead to pre-cancer (i.e., low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL)) and cancer. Cervical cancer can be prevented if it can be identified at an early stage. HPV vaccines can protect against the main high-risk HPV types, HPV 16 and 18, but they do not protect against all the high risk HPV types that can cause cervical cancer. Hence, regular cervical screening is still necessary.

The Pap test is the current test for identifying abnormalities in the cervix. In the Pap test, the cells are scraped from the cervix and examined for the presence of pre-cancer changes (LSIL and HSIL). However, this standard cytology method depends on visual assessment and is highly subjective with low sensitivity. Currently HPV testing is also performed on LSIL and HSIL cases and although this test has good sensitivity, its specificity is poor. Also, a positive HPV test result just indicates the presence of HPV DNA but does not indicate if the HPV infection is transient or persistent.

Thus, there is an unmet clinical need to develop new methods with good sensitivity and specificity to objectively identify patients who are at high risk of developing cervical cancer.

The overall objective of this project was to develop new methods based on Raman spectroscopy for probing biochemical changes associated with high risk HPV infection and dysplasia in cervical cells collected during routine Pap smear screening. During the project, a comprehensive Raman spectral library containing high-quality Raman spectra measured from cervical samples of >400 patients was established. HPV DNA (Cobas 4800 HPV test) and HPV mRNA testing (APTIMA HPV test) was also carried out on all samples. A chemometric model was developed that could predict high-risk HPV infection and pre-cancer stage and most importantly could distinguish between persistent and transient HPV infection. In addition to training through research, the MSCA fellow was trained in transferable skills such as project management, communication skills, networking, ethics, gender equality and IPR management.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

During the project, Raman spectra were collected from each sample in the biobank (n>400) and a comprehensive Raman spectral database of negative cytology and low grade (LSIL) and high grade (HSIL) cervical cytology samples was developed. It
was established that it was possible to detect pre-cancer related changes in the cervix by analysing the morphologically normal appearing superficial and intermediate epithelial cells in HSIL cytology samples using Raman spectroscopy and that excellent sensitivity and specificity could be achieved for identifying the HSIL cases based on the spectral dataset obtained from the intermediate cells, superficial cells and a mixed population of intermediate and superficial cells. Having established that morphologically normal appearing superficial and intermediate cells could be used, this procedure was then followed for the rest of the project. Histology and cytology results were obtained from the Coombe Women and Infants University Hospital and HPV DNA and mRNA assays were also performed. A chemometric model was developed which showed that negative and HSIL cases could be discriminated very well but that HPV results were necessary to discriminate the LSIL cases. HPV DNA-negative and HPV mRNA-negative LSIL cases (ie. HPV negative), HPV DNA-positive and HPV mRNA-negative LSIL cases (ie. transient HPV infection) and HPV DNA-positive and HPV mRNA-positive LSIL cases (ie. persistent HPV infection) were found to be three distinct groups. Thus, it was found that Raman spectroscopy could identify LSIL cervical cytology cases with a persistent HPV infection that were likely to progress to high grade pre-cancer or cancer and those with a transient HPV infection that were likely to regress.

A European patent application was filed on the basis of these findings. In addition, the results were presented at a number of conferences and one paper has been submitted to Scientific Reports and one further paper is currently in preparation.

Training-through-research was provided by the host laboratory and by the Molecular Pathology Laboratory in the Coombe Women and Infants University Hospital and training in transferable skills was provided throughout the MSCA fellowship. The MSCA fellow transferred knowledge in software development and multivariate analysis to the host laboratory members and also to the host’s wider research network.

Intersectoral transfer of knowledge was provided through a secondment at Dansk Fundamental Metrologi (DFM), Denmark. This allowed the researcher to experience working in a non-academic environment which has been very beneficial for her career development. At the end of the secondment, the researcher was offered a permanent Staff Scientist position at DFM.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

The results obtained during this MSCA fellowship have shown that the cellular biochemical fingerprint obtained using Raman spectroscopy can determine if a cell is positive for HPV and furthermore, if the HPV infection is persistent and the cell is at risk of progressing to pre-cancer. This new method based on Raman spectroscopy is a novel, cost-effective solution to distinguish between women with persistent low grade cervical abnormalities at risk of disease progression and those likely to regress. Currently there is an ongoing debate as to whether cytology (Pap tests) could be replaced by HPV testing for primary cervical screening. HPV infection is very common but will clear in most cases and will not lead to any adverse health effects. However, a persistent HPV infection can lead to an increased risk of cervical cancer in the future so these women need immediate treatment. This research has addressed an unmet clinical need to develop new methods to objectively identify patients with a persistent HPV infection who are at high risk of developing cervical cancer.

In addition to research training, and transferable skills training, the MSCA fellow also benefited from intersectoral training in the non-academic sector for her secondment. This resulted in a permanent Staff Scientist position for the MSCA fellow.

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